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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

OCT 9 1997

Federal Express

Bruce A. Hanna, Ph.D.
Department of Pathology
4N32 Bellevue Hospital
First Avenue and 27th Street
New York, New York 10016

Dear Dr. Hanna:

You were inspected during the period of May 1 through June 3, 1997, by Mr. Andrew Paglia, an investigator from the United States Food and Drug Administration's New York District Office. Mr. Paglia audited your [redacted] of the [redacted] sponsored by [redacted] that was reported in an application for premarket approval. This product is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approvals (PMA) or Premarket Notifications [510(k)] are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of the scientific investigation.

Title 21, Code of Federal Regulations (21 CFR) Part 812, Investigational Device Exemptions, and section 520(g) of the Act were used as guidance to audit your study. The deficiencies noted during the inspection were listed on a form FDA 483, "Inspectional Observations," which was presented to and discussed with you at the conclusion of the inspection. Our review of the inspectional report submitted by the district office raised significant questions concerning the conduct of your study. The following protocol deviations were noted during a review of eighteen patients' records:

You submitted a total of 1647 specimens from [redacted] study subjects to the sponsor. However, 374 specimens (502 assays) from 140 patients were excluded from data analysis by [redacted] because information that was submitted was incomplete or inaccurate as follows: 1) 224 specimens were excluded because specimen data was incomplete; 2) 109 specimens were not tested according to the protocol; 3) twenty-four specimens were not part of the study; 4) five specimens were excluded due to system error; 5) eleven specimens were excluded because no retesting was done; and 6) one specimen was an unnecessary repeat. Of 34 smear positive patients, only 15 smear positive patients were included in the data submitted in the PMA. Four smear positive patients ([redacted] and [redacted]) were excluded due to lack of [redacted] categorization. For the 140 patients who

were excluded from data analysis for the protocol deviations previously stated, case report forms (CRFs) #5 did not include a first patient in specimen study date as required in the bacteriology/virology section of the protocol.

The protocol states that only three specimens per subject are to be entered into the study. Eighteen study subjects were tested greater than three times (for a total of 157 specimens); data from these 157 samples were excluded from analysis. An additional 34 subjects who did not receive [redacted] classifications as required by the protocol were excluded from the analysis.

Retesting was not performed as required by section six of the protocol which states that retesting will be performed when invalid controls, instrument errors, initially reactive specimens are found, or gray zone/equivocal specimens are encountered. At least sixteen specimens should have been retested due to invalid run calibrations, system errors, or insufficient sample volume. The [redacted] instrument problem log was to be used to report these problems; however, there was no documentation that the log was utilized at your site.

CRFs for several patients were inaccurate as to treatments and dates of study entry. For example, record review for study subject [redacted] indicates a study entry date of 5/30/96 reported on the case report form. However, admission and discharge dates for subject [redacted] are 4/27/96 and 7/1/96, respectively. The initial clinical diagnosis section of CRF #5 indicates [redacted] not treated. However, review of patient charts indicated the patient had received drug treatment. Treatment status is an essential criteria for patient inclusion in the protocol and for data analysis.

Patient [redacted] was entered into the study on 3/30/96. The history/clinical data section of CRF #5 did not reflect a first patient specimen study date as required. A previous treatment with [redacted] was also omitted from the CRF and the patient was inappropriately categorized for treatment status and may have been inappropriately included in the data analysis. Similar discrepancies in data reporting were found during a review of CRFs and medical history records for patients [redacted] and [redacted]

The above protocol deviations and inaccurate information lead us to question the reliability of data in your clinical study. The above deviations are not intended to be an all-inclusive list of deficiencies which may exist in your clinical study. It is your responsibility to assure adherence to each requirement of the Act and regulations.

Please advise this office, in writing, within fifteen (15) working days of receipt of this letter of the specific steps you have taken to correct these violations and to prevent the recurrence of similar violations in current or future studies.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attn: Robert K. Fish, Consumer Safety Officer. A copy of this letter has been sent to our New York District Office, 850 Third Avenue, Brooklyn, New York. 11232. We request that a copy of your response be sent to that office.

Sincerely yours,

for Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health